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REVIEW

Should new oral anticoagulants replace low-molecular-weight heparin for thromboprophylaxis in orthopaedic surgery?

Les nouveaux anticoagulants vont-ils remplacer les HBPM en prévention thromboembolique en orthopédie ?

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Summary Current anticoagulant provision is dominated by parenteral low-molecular-weight heparin and oral vitamin K antagonists (VKAs), which indirectly inhibit several steps of the coagulation pathway. Two unmet needs for anticoagulation are safety and ease of use. Safety relates primarily to the incidence of major bleeding, which remains the key concern of orthopaedic surgeons and anaesthetists, over and above any efficacy advantage, and convenience of use, which centres on oral administration replacing the need for injections or monitoring platelets or coagulation with VKA. Recent research efforts towards identifying small-molecule inhibitors of coagulation enzymes as novel therapies for thrombotic disorders have been particularly successful in developing orally available molecules to directly inhibit the key proteases, factors IIa and Xa. Of the new oral anticoagulants in development, dabigatran etexilate (BIBR 1048) and rivaroxaban (BAY 59-7939), which inhibit factors IIa and Xa, respectively, are the most advanced and were approved in Europe in 2008. Based on the available data, we can conclude that dabigatran etexilate is non-inferior to enoxaparin in terms of efficacy and safety, and two different doses (220 and 150 mg/day) have now been approved. The 150 mg/day dose is intended for elderly patients and those with moderate renal impairment, which allows clinicians to decrease the risk of bleeding in the increasing number of fragile patients undergoing major orthopaedic surgery. In conclusion, rivaroxaban is superior in efficacy to enoxaparin, even with the US enoxaparin dosing regimen (30 mg b.i.d.), without significant differences in safety.
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MOTS CLÉS

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la thrombine ;
Orthopédie

Résumé Les HBPM, par voie sous-cutanée et les AVK par voie orale inhibent plusieurs facteurs de la coagulation permettant ainsi d'éviter l'extension d'un thrombus. Les recherches récentes ont permis de développer des nouvelles molécules synthétiques très spécifiques agissant sur un seul facteur de la coagulation en inhibant directement le IIa ou le Xa. Sur tous les nouveaux anticoagulants en développement, deux ont déjà l'AMM européenne et sont sur le marché en Europe : le dabigatran éxétilate, commercialisé (Pradaxa®) et le rivaroxaban (Xarelto®) qui inhibent respectivement le facteur IIa et Xa. Actuellement, les deux principaux apports que peuvent avoir ces nouvelles molécules sont essentiellement : la commodité d'emploi, apportée par la voie orale et l'absence de surveillance des plaquettes ou de la coagulation, mais aussi la tolérance au niveau du saignement, des effets hépatiques et coronariens. Le problème de tolérance devient primordial pour tous les cliniciens. Dans ce chapitre, ne seront traités que les deux anticoagulants déjà sur le marché européen : le dabigatran éxétilate et le rivaroxaban. Si on veut résumer le résultat de ces études : pour le dabigatran éxétilate, il existe une non-infériorité en termes d'efficacité et de tolérance en comparaison avec l'énoxaparine. Cependant, de façon beaucoup plus intéressante, pour la première fois, l'AMM a été accordée aux deux doses étudiées : 220 et 150 mg/j, réservant la dose réduite de 150 mg/j aux patients âgés de plus de 75 ans et insuffisants rénaux modérés. Enfin, une dose réduite, évaluée efficace peut être donnée en minimisant le risque de saignement chez cette population particulièrement fragile. Pour le rivaroxaban, il existe une supériorité en termes d'efficacité en comparaison avec l'énoxaparine, sans différence significative sur la tolérance, en termes de saignements majeurs. De plus, cette supériorité est retrouvée quel que soit le schéma d'utilisation de l'énoxaparine (40 mg/j en Europe et 30 mg deux fois par jour aux États-Unis). Enfin, cette supériorité existe aussi pour la première fois sur les événements symptomatiques dans deux études et dans la méta-analyse sur les quatre études.

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Abbreviations

ALT	alanine aminotransferase
CI	confidence interval
C _{max}	peak concentration
DVT	deep vein thrombosis
EMA	European Medicines Agency
PE	pulmonary embolism
RD	relative difference
RRR	relative risk reduction
THR	total hip replacement
TKR	total knee replacement
ULN	upper limit of the normal reference range
VTE	venous thromboembolism event

Introduction

Current anticoagulants for thromboprophylaxis have a number of limitations, including parenteral administration or unpredictable pharmacology that requires monitoring, and although they are effective, there remains room for improvement. Two unmet needs are safety and ease of use. Safety relates primarily to the incidence of major bleeding, which remains the key concern of orthopaedic surgeons and anaesthetists, over and above any efficacy advantage, and convenience of use, which centres on oral administration replacing the need for injections or monitoring platelets or coagulation with vitamin K antagonists (VKAs). Despite the recommendations against using aspirin [1,2], many patients still receive aspirin to prevent DVT simply because it is convenient. Therefore, new oral anticoagulants with

predictable pharmacology may be beneficial. Fondaparinux, the indirect activated factor X (factor Xa) inhibitor, provides proof of principle for pure factor Xa inhibition, but has the disadvantage that it is administered parenterally.

Recent research efforts towards identifying small-molecule inhibitors of coagulation enzymes as novel therapies for thrombotic disorders have been particularly successful in developing orally available molecules to directly inhibit the key proteases, thrombin (activated factor II; factor IIa) and factor Xa. Several anticoagulants are currently in development that target individual coagulation factors. The two agents in the most advanced stage of development are dabigatran etexilate (BIBR 1048) and rivaroxaban (BAY 59-7939), which inhibit factor IIa and factor Xa, respectively. Other agents in the early stages of development include several Xa inhibitors (LY-517717, YM150, DU-176b and apixaban [BMS-562247]), a factor IXa inhibitor (TTP889) and an orally active glycosaminoglycan enhancer (odiparcil [SB-424323]), which indirectly enhances thrombin inhibition via heparin cofactor II.

This review focuses on the results of trials of dabigatran etexilate and rivaroxaban that support the approval of the two drugs in thromboprophylaxis in orthopaedic surgery.

Similarities between phase-III studies

All trials were prospective, double-blind, double-dummy, randomized, multicentre studies in adults aged at least 18 years who were scheduled for primary elective total hip or knee arthroplasty.

The primary endpoints for the efficacy analysis were total VTE (the composite of DVT, non-fatal PE and all-cause mortality) and the composite of major VTE (venographic or symptomatic proximal DVT and PE) and VTE-related mortality. Bilateral venography was to be performed within 24 h of the last oral dose. All venograms were assessed centrally by adjudication committees who were blinded to treatment allocation and used the same protocol. PE was established by ventilation–perfusion scintigraphy, pulmonary angiography, spiral chest computed tomography or autopsy, depending on local preference. Symptomatic DVT was confirmed by compression ultrasound or venography and was assessed centrally by the same VTE-adjudication committee. Deaths were considered related to VTE if they were categorized as “VTE related” or “unexplained” by the independent adjudication committee.

The main safety endpoint was the frequency of major bleeding events occurring between the first dose of study medication and three days after the last dose. Secondary safety outcomes included the composite of major and clinically relevant non-major bleeding events, other bleeding events during treatment, liver enzyme elevation (above three times and above five times ULN for serum ALT) and acute coronary events (defined as confirmed unstable angina, myocardial infarction and cardiac death). Major, clinically relevant non-major and minor bleeding events were classified by the same independent expert adjudication committee. All outcomes were assessed by central independent adjudication committees blinded to treatment allocation.

Independent committees, blinded to treatment allocation, reviewed cases of hepatic enzyme abnormalities in which an ALT above three times ULN had occurred and any suspected acute coronary syndrome events. An assessment of causality was provided for each of the patient cases reviewed.

Concomitant administration of low-dose aspirin (<160 mg) and selective cyclooxygenase-2 inhibitors was allowed during treatment. Elastic compression stockings were permitted and intermittent pneumatic compression devices were prohibited.

About 25% of patients were excluded from the intention-to-treat population mainly because bilateral venography was not performed (usually declined by the patient) or the venograms were considered indeterminate by the venography adjudication committee.

Main differences between the two studies and the two anticoagulants

There were differences reflecting different regulatory requirements as well as variations in clinical practice between Europe and North America. According to the continent, the use of enoxaparin was different: 40 mg once daily starting before surgery or 30 mg twice daily starting 12–24 h postoperatively. In addition, there were differences in the duration of prophylaxis required following total hip or knee arthroplasty. In particular, the definition of major bleeding was different. In the dabigatran studies, bleeding occurring at the surgical site was considered major in accordance

with recommended guidelines, while in rivaroxaban studies, the major bleeding definition did not include surgical site bleeding.

The main differences and similarities between dabigatran and rivaroxaban are summarized in Table 1.

Dabigatran etexilate

Dabigatran etexilate (Pradaxa®), a novel, oral, reversible, direct thrombin inhibitor, is being investigated in several thromboembolic diseases and was approved by the EMEA in March 2008 for the prevention of VTE in adult patients undergoing elective THR or TKR. The onset and offset of its anticoagulant activity are rapid and predictable. The recommended time for initiating dabigatran etexilate treatment, based on its pharmacokinetic profile, is within 1–4 h postsurgery with only half a dose on the day of surgery. Absorption occurs slowly after the first postoperative dose (6 h), probably due to alterations in gastric motility after surgery. In view of the increased bleeding risk immediately following surgery, this slow and steady absorption profile in the early postoperative period might represent an advantage in that it reduces the risk of postoperative bleeding [3]. C_{\max} occurs about 6 h after the first dose, which means about 7–10 h after surgery. In the steady state, absorption occurs more rapidly and C_{\max} occurs about 2 h after administration.

In all the studies, two different doses of dabigatran (150 and 22 mg od) were compared to enoxaparin. The incidence of acute coronary syndrome events was similar between groups for the duration of the 3-month follow-up period. This observation, together with the lack of any significant between-group differences in PE or death during follow-up, suggests that there is no rebound effect (i.e., no hypercoagulable state after discontinuation of anticoagulant treatment) following completion of treatment.

Dabigatran etexilate can be given once daily without dose adjustments. A linear correlation exists between, ecarin clotting time particularly and with prothrombin time, thrombin clotting time, and plasma dabigatran concentration, confirming the predictability of the pharmacokinetics and pharmacodynamics of dabigatran. With the exception of individuals with significant renal impairment (creatinine clearance 30–50 mL/min), dose reduction is not needed in unique populations, such as obese patients or those from different ethnic backgrounds.

Dabigatran etexilate was as effective as enoxaparin for the primary prevention of VTE, with a similar safety profile, in the two phase III trials (RE-MODEL™ [4] and RE-NOVATE™ [5]) that led to approval in the European Union (Table 2). The primary efficacy endpoint (total VTE) was not reached in RE-MOBILIZE [6] because of the comparison between enoxaparin 30 mg twice daily with the same dose of dabigatran started later (6–8 days). However, there was no significant difference in major VTE and there was a trend to less major bleeding (0.6%) in the dabigatran group than in the enoxaparin group (1.4%).

A pooled analysis of major VTE was presented at the International Society on Thrombosis and Haemostasis meeting in 2007 [7]. The composite of major VTE (proximal DVT and/or PE) and VTE-related mortality occurred in 3.3% (69

Table 1 Drug characteristics.

	Dabigatran etexilate (anti-IIa)	Rivaroxaban (anti-Xa)
Approved by EMEA	March 2008	September 2008
Indications	Prevention of VTE in adults undergoing THR or TKR	Prevention of VTE in adults undergoing THR or TKR
Doses	150 mg/day if > 75 years otherwise 220 mg/day	10 mg/day
Administration	Oral o.d. Half dose the 1st day, started 4–6 h after the end of surgery	Oral o.d. Full dose 1st day, started 6–10 h after the end of surgery
Contraindications	Quinidine use Pregnancy, lactation Severe renal insufficiency Hepatic disease associated with coagulopathy	Pregnancy, lactation Azole antimycotics HIV protease inhibitors Severe renal insufficiency Hepatic disease associated with coagulopathy
Bioavailability (%)	6.5	80–100
Binding protein (%)	34–35	92–95
T _{max} (h)	2–4 6 the 1st day	2–4
Half-life (h)	14–17	7–11
Elimination	Urinary (85%) Faecal (6%)	Urinary (65%), but only 33% in active metabolites Faecal (35%)
Careful use	> 75 years Moderate renal impairment (CL _{CR} 30–50 mL/min) < 50 kg or > 110 kg Amiodarone	Cirrhotic with moderate hepatic impairment (Child Pugh B) without coagulopathy
Interaction	Quinidine	Azole-antimycotics HIV protease inhibitors
Monitoring	No	No
Antidote	Not available (dialysable)	Not available (not dialysable)

CL_{CR}: creatinine clearance; EMEA: European Medicines Agency; o.d.: once daily; THR: total hip replacement; TKR: total knee replacement; T_{max}: time to peak concentration; VTE: venous thromboembolism.

of 2096) of the enoxaparin group, 3.0% (62 of 2033) of the dabigatran etexilate 220 mg group (RD −0.2%, 95% CI −1.3 to 0.9%, $I^2 = 37\%$) and 3.8% (78 of 2071) of the 150 mg group (RD 0.5%, 95% CI −0.6 to 1.6%, $I^2 = 0\%$). Major bleeding occurred in 1.4% of the enoxaparin group, 1.4% of the dabigatran etexilate 220 mg group (RD −0.2%, 95% CI −0.8 to 0.5%, $I^2 = 40\%$) and 1.1% of the 150 mg group (RD −0.4%, 95% CI −1.0 to 0.2%, $I^2 = 0\%$). Most of the major bleeding events (80–90%) occurred at the surgical site. In the European trials, where the design was similar in terms of time of the first dose of enoxaparin and dabigatran etexilate, about half of the major bleeding events in the dabigatran groups (44% in the 220 mg group, 50% in the 150 mg group) occurred before any active drug was given.

The EMEA has decided that the 150 mg dose should be used in patients aged over 75 years or in individuals with moderate renal impairment (and if concomitantly treated with amiodarone) and the 220 mg dose for all other patients.

According to the latest American College of Chest Physicians guidelines [1], the low-molecular-weight heparin (LMWH) dose should be reduced in elderly patients or those with renal impairment, but without recommendation about the dose needed because no study currently shows that a lower dose of LMWH is efficacious in this population. With dabigatran, the 150 mg dose was studied in many patients and the efficacy was demonstrated with a trend to less major bleeding in this population [8]. The question now is how important is adherence to oral treatment? The half-life is 17 h in elderly patients, thus if the patients forgets or skips a dose 1 day after discharge, they are not at high risk of a thromboembolic event. Indeed, the risk is very high during the first 7 days (during which the patient is generally hospitalized) and decreases thereafter, especially in TKR. Furthermore, this population is used to taking several medications, and they often use a pillbox, which reduces the likelihood of missed doses.

Table 2 Phase III controlled, randomized, double-blind, studies of dabigatran etexilate.

	THR		TKR		Pooled analysis	
	RE-NOVATE		RE-MODEL	RE-MOBILIZE		
Study population	3494		2076	2615		
Treatment dosage and duration after surgery	Dabigatran 150 mg or 220 mg o.d. vs enoxaparin 40 mg o.d. 35 ± 4 days		Dabigatran 150 mg or 220 mg o.d. vs enoxaparin 40 mg o.d. 6–10 days	Dabigatran 150 mg or 220 mg o.d. vs enoxaparin 30 mg b.i.d. 10–14 days		
Dose group (mg)	150 220		150 220	150 220	150 220	
Total VTE (%)	8.6 vs 6.7 6.0 vs 6.7		40.5 vs 37.7 36.4 vs 37.7	33.8 vs 26.5* 31.1 vs 26.5*	3.8 vs 3.3 3.0 vs 3.3	
Major VTE (%)	4.3 vs 3.9 3.1 vs 3.9		3.8 vs 3.5 2.6 vs 3.5	3.0 vs 2.2 3.4 vs 2.2	—	
Major bleeding (%)	1.3 vs 1.6 2.0 vs 1.6		1.3 vs 1.3 1.5 vs 1.3	0.6 vs 1.4 0.6 vs 1.4	1.1 vs 1.4 1.4 vs 1.4	

b.i.d.: twice daily; o.d.: once daily; THR: total hip replacement; TKR: total knee replacement; VTE: venous thromboembolism.

* $p < 0.05$.

Rivaroxaban

Rivaroxaban (Xarelto®) is a novel, oral, direct factor Xa inhibitor. Phase II studies demonstrated that rivaroxaban was potentially safe and effective for thromboprophylaxis after major orthopaedic surgery across a wide dose range. Rivaroxaban total daily doses of 5–20 mg had similar efficacy to enoxaparin after THR and TKR, which probably means a very large therapeutic window. Several phase III studies with rivaroxaban 10 mg once daily have been published. RECORD 1, 2 and 3 compared rivaroxaban with enoxaparin 40 mg once daily. RECORD 1 and 2 compared extended rivaroxaban treatment to short-duration enoxaparin treatment in patients undergoing THR. RECORD 3 and 4 compared rivaroxaban to enoxaparin in patients undergoing TKR; RECORD 4 used the US-approved enoxaparin regimen. Details of these trials are described in Table 3.

THR: RECORD 1 and 2

Overall, RECORD 1 showed superiority for rivaroxaban, demonstrating a 70% RRR ($p < 0.001$) in total VTE compared with enoxaparin, and an 88% RRR ($p < 0.001$) in major VTE [9]. The superior efficacy of rivaroxaban was not associated with any significant differences in the incidence of major bleeding between the rivaroxaban and enoxaparin groups (0.3 and 0.1%, respectively, $p = 0.178$). Rivaroxaban was not associated with compromised liver function.

Overall, RECORD 2 demonstrated a 79% RRR in total VTE for extended rivaroxaban treatment ($p < 0.0001$) and an 88% RRR ($p < 0.0001$) in major VTE [10]. The superior efficacy of rivaroxaban was not associated with any significant differences in the incidence of major bleeding between groups ($< 0.1\%$ in both groups). Rivaroxaban was not associated with compromised liver function.

The main difference between RECORD 1 and 2 was the duration of prophylaxis in the enoxaparin arm. Indeed, in RECORD 2, enoxaparin was given for only 2 weeks, while rivaroxaban was given for 4 weeks. The results of both studies have shown superiority for rivaroxaban, as expected, but also significant superiority in preventing symptomatic DVT. More interestingly, there was no difference in major bleeding, even when enoxaparin was stopped after 2 weeks, which means that, the rate of major bleeding occur in the first days after surgery and rarely after discharge.

TKR: RECORD 3 and 4

Overall, RECORD 3 demonstrated a 49% RRR ($p < 0.001$) in total VTE for rivaroxaban compared with enoxaparin, and a 62% RRR ($p < 0.016$) in major VTE [11]. Most interestingly, there was a significantly lower rate of symptomatic DVT in the rivaroxaban group than in the enoxaparin group. The superior efficacy of rivaroxaban was not associated with any significant differences in the incidence of major bleeding between the rivaroxaban and enoxaparin groups (0.6 and 0.5% respectively, $p = 0.774$). Rivaroxaban was not associated with compromised liver function.

In RECORD 4, rivaroxaban 10 mg once daily was compared to the US-approved enoxaparin regimen of 30 mg injected twice daily. There was a 31% RRR in total VTE with rivaroxaban compared with enoxaparin, with a similar safety profile.

Table 3 Phase III controlled, randomized, double-blind, multicentre studies of rivaroxaban.

	THR		TKR		Pooled analysis
	RECORD 1	RECORD 2	RECORD 3	RECORD 4	
Study population	4541	2059	2531	3148	
Treatment dosage and duration after surgery	Rivaroxaban 10 mg o.d. vs enoxaparin 40 mg o.d. started the day prior to surgery 35 ± 4 days	Rivaroxaban 10 mg o.d. vs enoxaparin 40 mg o.d. started the day prior to surgery 35 ± 4 days	Rivaroxaban 10 mg o.d. vs enoxaparin 40 mg o.d. started the day prior to surgery 12 ± 2 days	Rivaroxaban 10 mg o.d. vs enoxaparin 30 mg b.i.d. started 12–24 h after surgery 12 ± 2 days	
Total VTE (%)	1.1 vs 3.7*	2.0 vs 9.3*	9.6 vs 18.9*	6.9 vs 10.1*	—
Major VTE (%)	0.2 vs 2.0*	0.6 vs 5.1*	1.0 vs 2.6*	1.2 vs 2.0	—
Symptomatic VTE (%)	0.4 vs 0.7	0.4 vs 1.7*	1.0 vs 2.7*	0.7 vs 1.2	0.47 vs 0.97*
Major bleeding (%)	0.3 vs 0.1	0.1 vs 0.1	0.6 vs 0.5	0.7 vs 0.3	—

b.i.d.: twice daily; o.d.: once daily; THR: total hip replacement; TKR: total knee replacement; VTE: venous thromboembolism.
* $p < 0.05$.

Both treatments were continued for 10–14 days. Top-line results from this study were first presented in May 2008 at the annual meeting of the European Federation of National Associations of Orthopaedics and Traumatology.

The results of a prespecified pooled analysis to evaluate the effect of rivaroxaban on the composite of symptomatic VTE and death, as well as bleeding, was presented by Turpie et al. at the American Society of Haematology meeting [12]. These primary outcomes were analysed at day 12 ± 2 in the active treatment pool (i.e., during the enoxaparin-controlled period common to all studies, to allow for unbiased comparison with enoxaparin) and for the total study duration pool (planned treatment period and 30–35 days of follow-up). Rivaroxaban reduced the incidence of symptomatic VTE and all cause of mortality significantly compared with enoxaparin at day 12 ± 2 (0.47% vs 0.97%, $p = 0.001$) and for the total study duration (0.81% vs 1.63%, $p < 0.001$). Rivaroxaban was not associated with a statistically significant increased risk of major bleeding. Most interestingly, the combined criteria of death, symptomatic VTE, myocardial infarction, stroke and major bleeding, was significantly lower in the rivaroxaban group compared with the enoxaparin group ($p = 0.004$).

Conclusions

These new oral anticoagulants feature some major advantages over traditional anticoagulants, including no requirement for anticoagulant monitoring, a low drug–drug interaction potential and the possibility to use in both the acute and chronic settings. These drugs provide an alternative to subcutaneous enoxaparin for the prevention of VTE after THR and TKR. Rivaroxaban demonstrated superior efficacy over enoxaparin even in symptomatic DVT, without significant differences in major bleeding. Dabigatran etexilate is the first anticoagulant registered and approved by the EMEA with two different doses and, for the first time, one reduced dose is defined for the elderly population or for patients with moderate renal insufficiency.

A report from the UK National Health Service indicates that only about half of patients undergoing major orthopaedic surgery who are at high risk of thromboembolic complications receive effective thromboprophylaxis. Although aspirin is not recommended [1], it is overused in many countries because its oral form makes it convenient. The approval of dabigatran etexilate and rivaroxaban has the potential to greatly improve this situation, as they have several advantages over current treatments: they are oral drugs that can be easily administered in hospital and after discharge, and offer the prospect of a longer duration of prophylaxis with higher adherence. The main interest will probably be to improve the prescription and the adherence to an effective thromboprophylaxis regimen for medical issues such as atrial fibrillation without the bleeding side-effects seen with LMWH or the coagulation monitoring required with VKA treatment.

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